Antifungals and Drug Resistance

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Contributor: Chowdhury Mobaswar Hossain , Lisa Kathleen Ryan , Meeta Gera , Sabyasachi Choudhuri , Nazmun Lyle , Kazi Asraf Ali , Gill Diamond

Antifungal drugs prevent topical or invasive fungal infections (mycoses) either by stopping growth of fungi (termed fungistatic) or by killing the fungal cells (termed fungicidal). Antibiotics also prevent bacterial infections through either bacteriostatic or bactericidal mechanisms. These microorganisms successfully develop resistance against conventional drugs that are designed to kill or stop them from multiplying. When a fungus no longer responds to antifungal drug treatments and continues to grow, this is known as antifungal drug resistance. Bacteria have an amazing capacity to become resistant to antibiotic action as well, and the effectiveness of the scarce antifungal arsenal is jeopardised by this antibiotic resistance, which poses a severe threat to public health.

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More than one billion people worldwide suffer from fungus-related illnesses known as mycoses each year, but their contribution to the world's disease burden is mostly unrecognized [1]. In 2020, an estimated 1.7 million fatalities from fungal infections were reported [2]. Healthcare practitioners have a tremendous dilemma in choosing anti-fungal agents as the prevalence of fungus infections rises alarmingly. This rise is directly linked to the rise in the number of immunocompromised people as a result of changes in medical practice, such as the use of powerful immunosuppressive medications and intense chemotherapy [3]. In the human microbiota, there are microbes like Candida spp. that can cause opportunistic infections in healthy people and life-threatening infections (invasive candidiasis) in people with weakened immune systems, like those with HIV, cancer patients receiving chemotherapy, and people taking immune-suppressive medications [4]. In addition to opportunistic and systemic infections, individuals with underlying disorders may develop healthcare-associated infections from fungal pathogens such Candida, Aspergillus, Fusarium and Mucorales. Systemic fungal infections frequently result from the genera Candida, Blastomyces, Coccidioides, Paracoccidioides, Histoplasma and Cryptococcus. The fourth most frequent opportunistic infection in hospitals is C. albicans infection [5]. Despite the use of antifungal treatments, invasive candidiasis (IC) is deadly in about 42% of instances that have been recorded. Currently, azoles like fluconazole, itraconazole, voriconazole (VOR), posaconazole and isavuconazole (ISV), polyenes like amphotericin B (AMB), and echinocandins like caspofungin, micafungin, and anidulafungin are the most often used antifungal medications for IC [6][7][8].

Different components of the fungal cell are affected by these antifungal substances. Azoles stop the formation of ergosterol, the primary building block of fungal membranes [7][9]. Echinocandins act by inhibiting the formation of 1,3-β-D-glucan found in the fungal cell wall, while polyenes like AMB interact with ergosterol-producing pores in the cell membrane. Resistance to Candida spp. has risen as a result of the progressive rise in the likelihood of infection with Candida and the increased use of antifungal medications [10]. The issue of antifungal resistance and

its molecular underpinnings has received interest due to pharmacological shortcomings in therapies for Candida spp. As a result, the current chapter offers a summary of prospective anti-fungal medicines, their mode of action, and their resistance.

1.1. Classification of Fungal Infections (Mycosis)

Mycosis are traditionally divided into four forms:

1. Superficial infections
2. Subcutaneous infections
3. Systemic infections

1.1.1. Superficial Infections

These are defined as an infection that mostly affects the stratum corneum, or the skin's outermost layer, as well as the mucous membranes, nails and hair. These infections, including those caused by Dermatophytes, Trichophyton spp., Microsporum spp., and Epidermophyton spp., are among the most prevalent diseases that people experience worldwide [11]. Transmission of the fungus occurs by direct contact with infected persons, animals, soil, or termites. Globally, 20–25% of the population is thought to have superficial mycoses, and the prevalence is increasing [12]. We can better understand future epidemiologic trends and risk factors for superficial fungal infections when we are aware of the primary causative species. Tinea capitis is a common condition of the skin that usually affects children older than six months. Tinea versicolor, an infection of the stratum corneum, is brought on by Malassezia spp. including M. furfur, M. globosa and M. sympodialis, a yeast that lives on the skin as a commensal. Onychomycoses, or nail infections, are thought to be the cause of 50% of all nail disorders and 33% of all fungal skin infections [13].

1.1.2. Subcutaneous Fungal Infections

The "subcutaneous" mycoses are caused by a wide variety of diverse organisms that can spread disease when implanted or otherwise introduced into the dermis or subcutis. Mycetoma, sporotrichosis, and chromoblastomycosis are the three kinds of subcutaneous mycoses [14]. They all seem to be brought on by causing trauma to the subcutaneous tissue where the etiological fungus is located. Verrucoid skin lesions are the hallmark of the subcutaneous mycosis known as chromoblastomycosis, which typically affects the lower extremities. The disease-specific "copper penny" cells, or muriform cells with perpendicular septa, are identified through histological analysis. Chromoblastomycosis usually only affects subcutaneous tissue and seldom affects bone, tendon, or muscle [15]. Mycetoma, on the other hand, is a subcutaneous mycosis that ravages nearby bone, skeletal muscle, and tendons. It is suppurative and granulomatous. Small, visibly coloured grains or granules are discharged from sinus tracts that form as a result of mycetoma. Sporotrichosis is the third broad category of subcutaneous mycoses. At the site of the traumatic inoculation, the infection brought on by Sporothrix schenckii affects the subcutaneous

tissue. The infection typically spreads through the affected extremity's cutaneous lymphatic pathways [16].

1.1.3. Systemic Fungal Infections

Systemic mycoses are the systemic infections predominantly caused by organisms from the genera Candida, Aspergillus and Mucor. In addition, disseminated infections from *Blastomyces*, *Coccidioides*, *Paracoccidioides*, *Histoplasma* and *Cryptococcus* spp. are also found [17]. Systemic mycoses enter the body by a deep focus or an internal organ such the paranasal sinuses, digestive tract, or lungs. The infection often starts in the lungs before spreading to the skin and other organs. Usually, the infection starts in the lungs before spreading to the skin and other organs. All of these organisms, with the exception of *Cryptococcus neoformans*, are dimorphic, forming as mycelia in their natural state and converting into yeast form in tissues. As a result, there is no additional discussion of the yeast infections that cause cryptococcosis in this section. Numerous lung illnesses and a localised skin affliction have been connected to *Chrysosporium parvum*, a filamentous soil saprophyte.

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